Medical and Pediatric Oncology 29:67–71 (1997)

PROCEEDINGS OF THE TUMOR BOARD CHILDREN'S HOSPITAL OF PHILADELPHIA

Giulio J. D'Angio, MD, Series Editor, and Audrey E. Evans, MD, Associate Editor

Late Recurrence of a Brain Tumor

Michael N. Needle, MD,[1] Lucy B. Rorke, MD,[2] and Peter Winkler, MD[3]

Key words: teratoma; intracranial carcinoma; primitive neuroectodermal tumor

Michael N. Needle, MD (Pediatric Neuro-Oncologist)

This case concerns a 32-year-old woman first seen at this hospital at the age of 9. At that time she presented with personality changes over several months and a left-sided hemiparesis of short duration. A cerebral angiogram demonstrated a large right temporal lobe mass, and at surgery, a tumor measuring 4 cm in diameter was completely removed. The pathologic diagnosis was malignant teratoma. The child was treated with 51 Gy to the right temporal lobe using 2 MeV photons.

She apparently fared well, and at age 19 a CT scan showed no evidence of tumor. One year later she developed episodes of staring and chewing movements. Initially they were not reported by the patient, but when brought to medical attention she was started on phenytoin. She subsequently developed a rash and was switched to valproic acid. A number of MRIs were done at this time, and none revealed tumor until three months prior to her recent presentation, when a lesion was noted distant to the original operative site. A repeat scan 3 months later (22 years after the first craniotomy) revealed that the right occipital-temporal mass was growing.

Peter Winkler, MD (Fellow, Neuro-Radiology)

We have an MRI performed 2 years ago. On the T2-weighted image, there is a large area below the glomus that is either intraventricular or in the wall that at most is only suspicious of a lesion. It is best seen with the "retrospectoscope." Eighteen months ago, the same area appeared questionably larger, but now there is obvious growth of an enhancing tumor (Fig. 1). Again, it is not clear whether this is intraventricular or paraventricular in the temporal lobe. The lesion is marked by hemorrhage or calcification.

Luis Schut, MD (Pediatric Neuro-Surgeon)

This is considerably distant from the original site, which was the anterior temporal lobe.

Dr. Needle. An exploration was considered necessary and the tumor was again excised completely via a right occipital-temporal craniotomy. Postoperatively, the patient's major finding is a left homonymous hemianopia, denser superiorly than inferiorly. The patient has been prescribed a 30 diopter base-out prism over the left half of the left lens.

Lucy Rorke, MD (Pediatric Neuro-Pathologist)

The lesion in 1961 showed nests of cells with central necrosis (Fig. 2A). Looking at only the histopathology, one could easily make the diagnosis of comedo carcinoma of the breast, which has this appearance. At that time, the best diagnosis was teratocarcinoma. Of course, the lesion is not really teratomatous being monophasic insofar as cellular type is concerned. The individual nests are sharply marginated, of varying size, and are distributed within a vascular stroma, the many vessels being thin-walled (Fig. 2B). Paraffin blocks were available and immunoperoxidase stains were performed on both the old and the new lesions. The tumor nests were negative for all markers, but the stroma was strongly positive for vimentin and keratin. All markers for germ cell tumors were negative. The lesion had a low mitotic index. The proliferating cell nuclear antigen (PCNA) stain was negative in the first lesion, but it is not known whether this is a function of the long period of time that elapsed between the operation and the application of the antibody; this could be a false-negative result. I mention this because the current lesion is homogeneous, consisting of a population of monotonous small round cells, some of which arrange themselves around vessels (Fig. 3A). Now,

[1]Division of Pediatric Neuro-Oncology and the [2]Departments of Pathology and [3]Radiology, The Children's Hospital of Philadelphia, Pennsylvania.

Correspondence to: Giulio J. D'Angio, MD, Department of Radiation Oncology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

Received 16 March 1995; Accepted 5 May 1995.

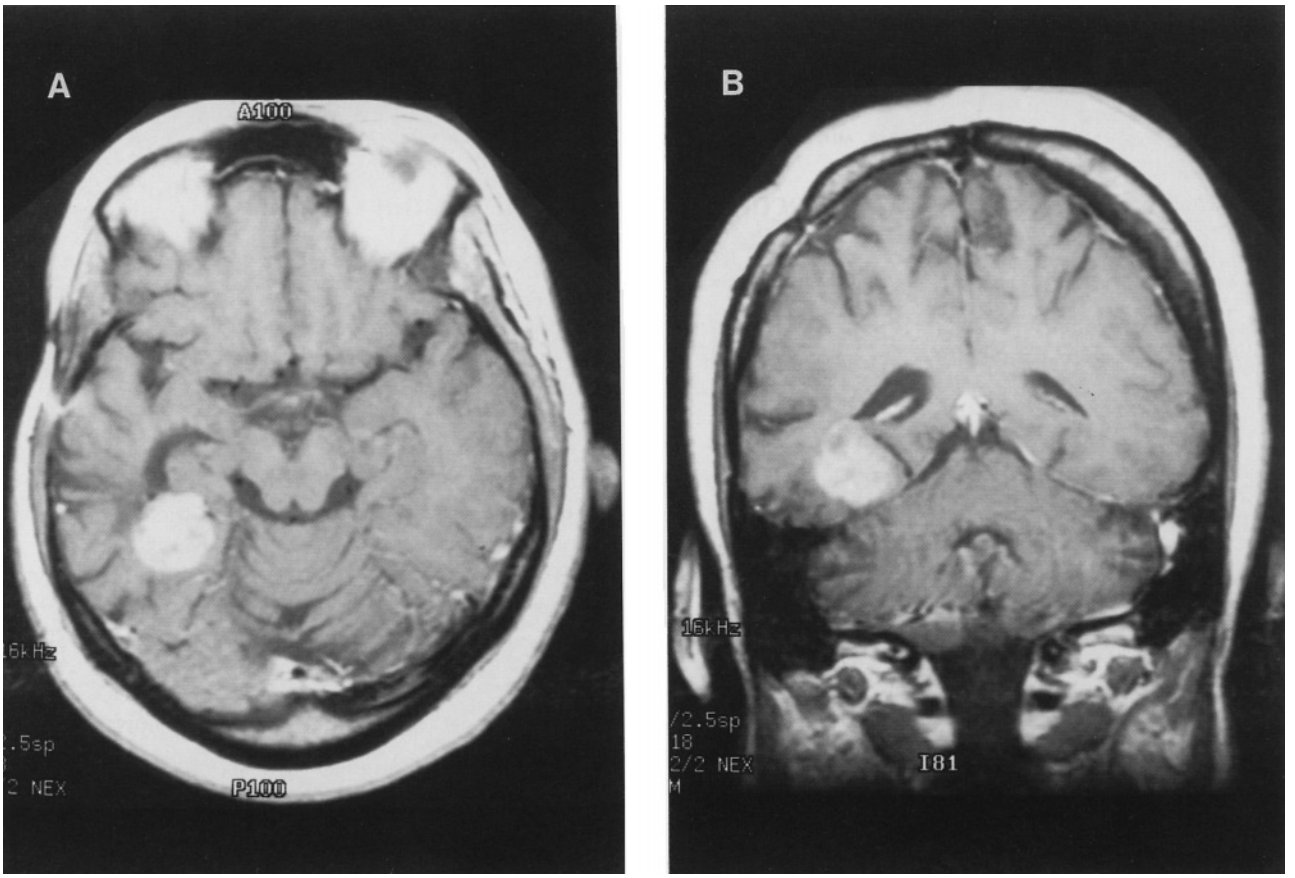

Fig. 1. T1 weighted gadolinium-enhanced images of the brain (**A:** axial; **B:** coronal) at the time of recurrence and prior to second craniotomy. A 2 cm in diameter enhancing lesion can be seen in the right occipital-temporal lobe.

the keratin stain is positive, the vimentin negative, whereas PCNA is strongly positive, the mitotic index being very high (Fig. 3B). The mesenchymal component has disappeared and only the epithelial part remains, so the best diagnosis I can attach to the lesion at this time is carcinoma.

Many questions remain as to the oncogenesis of the original, unique lesion, and the long interval between the primary and what at this recurrence appears to be a carcinoma of the brain.

Dr. Needle. It is curious that, as so often happens, another similar case came to Dr. Rorke's attention as we were working up to this woman. A 9-year-old boy presented to this hospital in 1959 because of headache and seizures. A tumor was diagnosed and a craniotomy was done. The pathologist at the hospital at that time called the tumor a malignant glioma. We have no records regarding any further therapy. This year the patient, now 43 years of age and living in Florida, presented with symptoms consistent with recurrence. MRI revealed a tumor, and he had a second operation for removal. Dr. Rorke was contacted by the pathologist in Florida. Perhaps you would comment, Dr. Rorke?

Dr. Rorke. The original slides and blocks were retrieved from the files and new sections were cut for staining by immunoperoxidase techniques. The two neoplasms in this patient were identical and more accurately placed in the category of primitive neuroectodermal tumor (PNET). In this instance, however, the PCNA index in the 1959 specimen was high. This suggests that the lack of staining for PCNA in the tumor of the first patient is a valid result and not a false negative.

Dr. Needle. Returning to our present patient, we need to make some management decisions. Although it is impossible to be certain whether this is a second malignant neoplasm or a recurrence, the rarity of the pathology leads me to believe that this is a recurrence. The only concerning feature is the change in the PCNA staining. The patient is now free of disease, both by surgeon's impression and postoperative gadolinium enhanced MRI. One question is the role of re-irradiation of the tumor bed. Dr. Goldwein, what is your opinion?

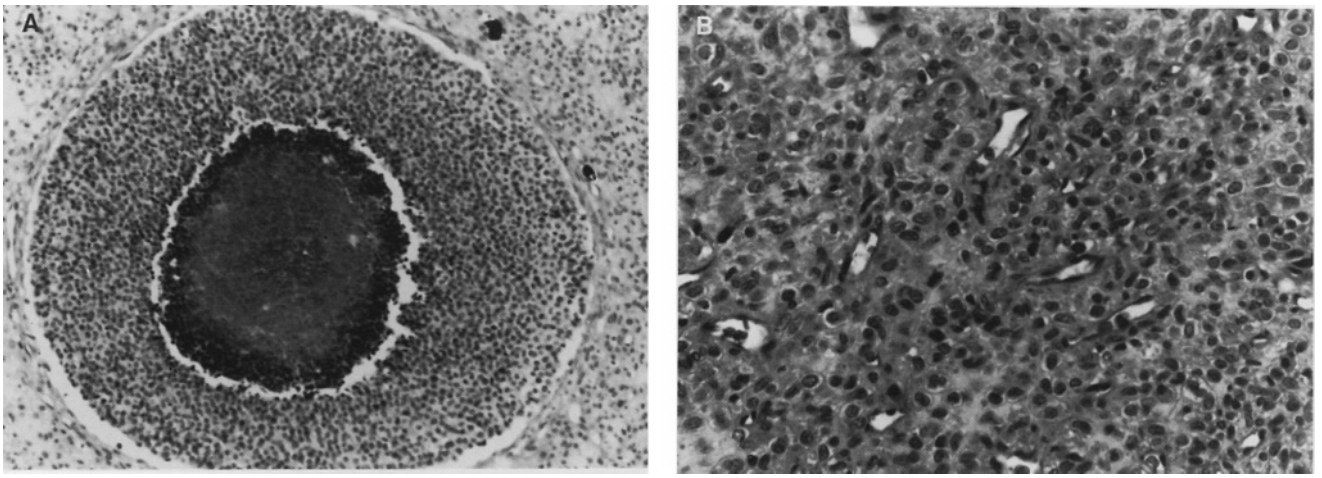

Fig. 2. **A:** Typical nest of epithelial cells with central necrosis in the first biopsy resembling comedocarcinoma of breast. **B:** Typical field of tumor adjacent to the epithelial nests pictured in A. Note prominent vascular component (H&E).

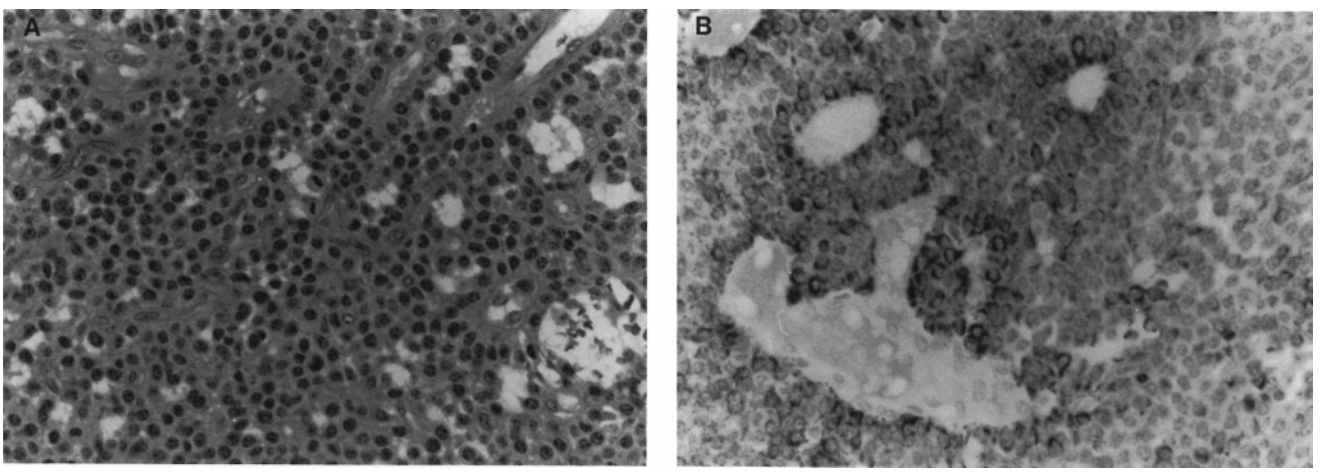

Fig. 3. **A:** Second biopsy showing shreds of small epithelial cells with small round nuclei, a variably-sized perikaryon and distinctive cell borders. Note tendency of the tumor cells to arrange themselves around blood vessels. Mitotic figures are present in the center of the field (H&E). **B:** Second biopsy showing presence of keratin in the tumor cells. Immunoperoxidase stain for AE1-K.

Joel Goldwein, MD (Pediatric Radiation Oncologist)

Nothing is known about the first course of treatment; neither the placement of the fields nor the dose. One might assume that 50–60 Gy was given. Reirradiation is contraindicated because the role of radiation therapy in these tumors is not well defined and because additional doses in a meaningful range would very likely lead to brain necrosis.

Giulio J. D'Angio, MD (Pediatric Radiation Oncologist)

I agree that it would be very risky to add radiation in the face of these major unknowns. For curiosity, were there any postradiation changes visible in the specimen, Dr. Rorke?

Dr. Rorke. No.

Dr. Schut. In view of that, is there any room here for brachytherapy, or possibly the implantation of chemotherapy-impregnated pledgets, which has been used in some centers with encouraging results? There is no room for surgery; the patient is already hemianopic. Also, is it possible she has a primary lesion somewhere and this is an unrelated metastatic deposit?

Anna Meadows, MD (Pediatric Oncologist)

A search for another and different primary tumor is in process. What if she were given no additional therapy? It's been a long interval since the first lesion, and she may well remain tumor-free for a similarly long interval.

Dr. Needle. Unfortunately, there is very little to guide us in exceptional cases such as these. The staging workup did not reveal a primary lesion, which brings us back to planning therapy for a patient with an unusual, recurrent malignant tumor of the brain. She has had the benefit of maximal surgery and is not a good candidate for radiation therapy. There is some comfort to be taken in the long interval between the original lesion and the recurrence, but the circumstances are not exactly the same. Not only do we no longer have radiation therapy as an option, but there may be a phenotypic change in that the primary tumor had a low PCNA, the recurrence a high PCNA.

A review of the literature did not reveal a case such as this, but there is information concerning the incidence and the implication of late recurrence in some common cancers, primarily of adulthood, such as Hodgkin disease [1]. Another example is a study of late local recurrence after "lumpectomy" for breast carcinoma reported by Kurtz. There were 178 local recurrences among 1,593 consecutive patients with clinical stage I–II disease treated with "lumpectomy" and radiation [2]. Of the 178 patients, 101 relapsed prior to the 5th year, and 71 thereafter. The early relapses were less likely (83%) to be operable (locally invasive) and less likely to be distant (14%). By contrast, the late relapses were almost always operable (99%) but were more commonly distant from the primary tumor (32%). Both of these differences were statistically significant. Actuarial survival also differed with the late recurrences having an 84% 5-year survival and the early recurrences a 61% 5-year survival. This difference was not statistically significant.

Unfortunately, not all late relapses carry a good prognosis. A case-control analysis of malignant melanoma patients with late relapses was reported by Calloway et al. [3]. Thirty-five patients who relapsed 6–20 years after primary treatment were matched to control patients who relapsed at 4–56 months [4]. The subsequent course from the time of recurrence was identical in the two groups. These data are presented to demonstrate that there are contradictory results in more common tumors, not to indicate that the results cited can in any way be related to tumors of the central nervous system.

The upshot is that, at this point, we have elected to follow this patient without adjuvant therapy. The decision was made for a variety of reasons. Primary was the uncertainty of the natural history of this process in this person. The tumor has displayed a biological behavior that is remarkable, i.e., the long interval of quiescent disease. One could therefore surmise that the course will continue to be indolent.

A second factor is the unusual histologic diagnosis. This patient is unique as near as I can tell, and there is no published experience to help us arrive at a therapeutic decision. Under these circumstances one would be submitting the patient to certain toxicity for uncertain benefit. The lack of measurable disease further complicates matters by removing the possibility of a therapeutic trial. How would one judge response? Interval to progression? Based on this patient's history, we may not be able to evalute the therapeutic intervention for 20 years!

Finally, the rarity of this case makes it unlikely that knowledge gained from treatment would be of benefit to another patient. There thus appear to be more reasons for observing this patient than for embarking on therapy.

Addendum

Workup for tumor elsewhere was negative, and the plan to follow the patient without adjuvant therapy was maintained. The patient developed recurrent tumor 2 years later, and has undergone repeat surgery.

REFERENCES

1. Bodis S, Henry-Amar M, Bosq J, Burgers JMV, Mellink WAM, Dietrich PY, Dupouy N, Noordijk EM, Raemaekers JMM, Thomas J, Eghbali H, Regneir R, Tanguy A, Verdonck L, Michel J, Zittoun R, Kerkhofs H, Hayat M: Late relapse in early-stage Hodgkin's disease patients enrolled on European Organization for Research and Treatment of Cancer protocols. J Clin Oncol 11:225–232, 1993.
2. Kurtz JM, Spitalier JM, Amalric R, Brandome H, Ayme Y, Jacquemier J, Hans D, Bressac C: The prognostic significance of late local recurrence after breast-conserving therapy. Int J Rad Onc Biol Phys 18:87–93, 1990.
3. Callaway MP, Briggs JC: The incidence of late recurrence (greater than 10 years); an analysis of 536 consecutive cases of cutaneous melanoma. Br J Plast Surg 42:46–49, 1989.
4. Tahery DP, Moy RL: Lack of predictive factors in late recurrence of stage I melanoma. Int J Dermatol 31:629–631, 1992.
5. Marshall FL, Rorke LB, Schut L: Teratocarcinoma—A treatable disease? Child's Brain 5:96–102, 1979.

Series Editor's Note

The tumor recurred in the occipital-temporal region of the brain. The names of parts of the brain are sometimes intriguing. *Temporal* has been discussed here before (Med Pediatr Oncol 20:366, 1992). *Occiput* is straightforward; it is the Latin term of that part of the skull from *ob* = against + *caput* = head. *Pons* (Latin = bridge) is an appropriate name for that portion of the hind brain containing crossing as well as longitudinal fibers. It is also known as the *pons Varolii*, named for the Italian anatomist Costanzo Varoli (or Varolio) (1543–1575). The term is applied to other anatomic parts, e.g., *pons hepatis*, but scarcely used in any other connection.

Pons is also the root of *pontiff*, meaning a bishop but usually restricted to the bishop of Rome, i.e., the pope (from Greek *pappas* via Latin *papa* = father). *Pontiff* is a variation of the French *pontife* derived from Latin *pontifex* (*pontem* = bridge + *facere* = to make). Thus *pontifex* indicates *bridge-maker.* It was applied to the five members of the principal college of priests in ancient Rome. For them, it had a literal significance, for they were in charge of the bridge crossing the Tiber. The chief priest was the

Pontiff Maximus, a term still used for the reigning pope. *Reign* (Latin: *regere* = rule) connotes more than royal power; it is applied also more generally to indicate authority (from the Greek *authentos* = "one who does things himself"). A similar meaning is conveyed by *sovereign,* an interesting blend of the Latin *super* + *reign,* and therefore quasi-tautologous (Greek: *tauto-*, a combination form signifying "the same").

Medulla (Latin = marrow, pith) *oblongata* (Latin = rather long) are more straightforward. *Medulla* itself perhaps echoes (Greek *ēchē* = sound) *medius* (middle), and the *medulla* (marrow) of bone is thereby explained. *Pith* (Old English: *pipa*) has a botanical (Greek: of herbs) origin, where *marrow* also fits, since it is the name for an edible gourd. Thus we have another word to link the dinner and dissecting tables, in addition to some noted earlier in these pages, e.g., Med Pediatr Oncol 18:67, 1990; 21:450, 1993.